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Oxidative Addition, Transmetalation, and Reductive Elimination at a 2,2'-Bipyridyl-Ligated Gold Center

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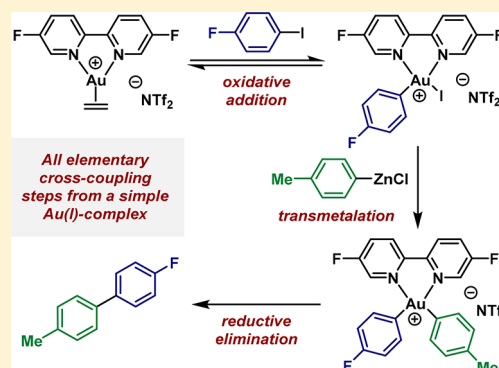
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Supporting Information

ABSTRACT: Three-coordinate bipyridyl complexes of gold, $[(\kappa^2\text{-bipy})\text{Au}(\eta^2\text{-C}_2\text{H}_4)][\text{NTf}_2]$, are readily accessed by direct reaction of 2,2'-bipyridine (bipy), or its derivatives, with the homoleptic gold ethylene complex $[\text{Au}(\text{C}_2\text{H}_4)_3][\text{NTf}_2]$. The cheap and readily available bipyridyl ligands facilitate oxidative addition of aryl iodides to the Au(I) center to give $[(\kappa^2\text{-bipy})\text{Au}(\text{Ar})\text{I}][\text{NTf}_2]$, which undergo first aryl-zinc transmetalation and second C–C reductive elimination to produce biaryl products. The products of each distinct step have been characterized. Computational techniques are used to probe the mechanism of the oxidative addition step, offering insight into both the origin of the reversibility of this process and the observation that electron-rich aryl iodides add faster than electron-poor substrates. Thus, for the first time, all steps that are characteristic of a conventional intermolecular Pd(0)-catalyzed biaryl synthesis are demonstrated from a common monometallic Au complex and in the absence of directing groups.



INTRODUCTION

The development of the chemistry of gold has been one of the most striking research themes of recent times. However, despite the promise implied by the diagonal relationship between Au and Pd, processes that imitate conventional Pd-catalyzed biaryl formations (Negishi, Suzuki, etc.) are lacking.¹ This is readily explained by the “redox gold problem”,² where the relative reluctance of gold to partake in $\text{M}^{x/x+2}$ redox processes (E^0 : $\text{Pd}^{\text{II}/0} = 0.92$ V, $\text{Au}^{\text{III}/\text{I}} = 1.41$ V) renders oxidative addition challenging.³ Notwithstanding this apparent obstacle, such processes remain highly desirable, primarily because of the biocompatibility of gold versus the toxicity of palladium. Furthermore, the idiosyncratic properties of gold, especially its unique functional group tolerance and Lewis acidity, hold the promise that known Pd-catalyzed processes will not simply be replicated, but that milder transformations, offering broader substrate scope and/or unusual selectivity, will be discovered.

The putative steps in a potential redox gold cycle are analogous to those of Pd(0)-catalyzed cross-couplings, consisting of oxidative addition, transmetalation, and reductive elimination (Scheme 1A).⁴ Of these, it is recognized that the oxidative addition step is challenging, due to the “redox gold problem” outlined above. Most commonly this is circumvented by employing an external oxidant, which facilitates the $\text{Au}(\text{I}) \rightarrow \text{Au}(\text{III})$ transformation and allows the catalytic coupling of two formally nucleophilic partners;^{5,6} however, the requirement of a

strong external oxidant limits the attractiveness of this strategy. Accordingly, extensive efforts have been devoted to the identification of oxidative addition processes that might allow the routine exploitation of internal oxidants (e.g., aryl halides) in Au catalysis. Three distinct strategies have emerged to facilitate the oxidative addition step: (a) the use of directing groups,^{7,8} (b) the use of highly electrophilic initiation motifs (e.g., allylic bromides, aryl diazoniums, $\text{CF}_3\text{-I}$),^{9–13} and (c) modification of the ancillary ligand on Au.¹⁴ The latter option is most attractive, as it potentially offers the greatest substrate scope; however, this avenue is also the least developed and most challenging. Of specific relevance is the work of Amgoune, Bourissou, and co-workers, who employed a bulky carboranyl diphosphine ligand that subtends a bite angle of approximately 90° at the Au center.¹⁴ This results in Au(I) complexes that express enhanced π -back-donation¹⁵ and undergo facile *nondirected* oxidative addition of both strained C–C bonds^{12b} and aryl iodides (Scheme 1B).¹⁴

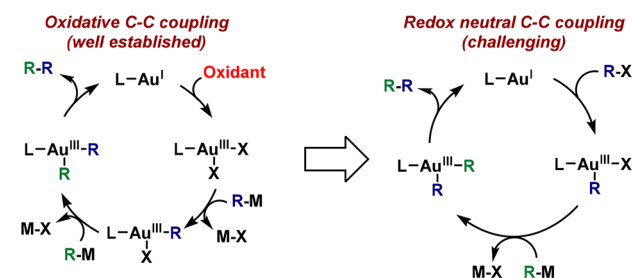
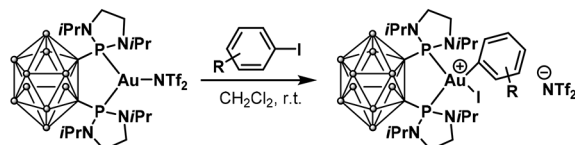
Clearly, the evolution of redox gold catalysis will be facilitated by gaining an in-depth understanding of fundamental steps that might underpin a possible catalytic cycle.¹⁶ Although the process in Scheme 1B is unique in its ability to promote efficient nondirected oxidative addition of aryl iodides,

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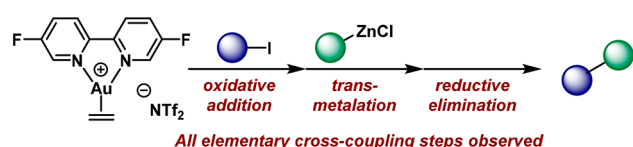
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Scheme 1

(A) Oxidative vs redox neutral Au-catalyzed cross-couplings:

(B) Modification of the ancillary ligand allows efficient Ar-I oxidative addition:¹⁴

(C) Negishi-type cross-coupling at a bipyridyl-ligated Au(I)-center (this work):

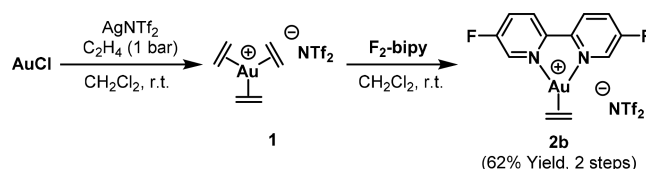


downstream cross-coupling steps (i.e., transmetalation and C–C reductive elimination) were not achieved.¹⁴ Indeed, while several elementary organometallic processes have been substantiated for gold only recently,¹⁶ there are no reports where all steps of a possible intermolecular biaryl forming cross-coupling cycle have been demonstrated from a common monometallic Au complex. In this article, we show how manipulation of the ligand environment at gold allows the sequential observation of oxidative addition, transmetalation, and reductive elimination from the same species (Scheme 1C). Remarkably, this is all achieved using the commonplace 2,2'-bipyridyl ligand (bipy) or its derivatives. Bipy has been employed as an additive in several exciting reports on gold catalysis,^{10c,e,f} although its precise function has not been established; we suggest that this role might be revisited in light of the results described herein.

Following the submission of this article, Amgoune, Bourissou, and co-workers published a Au(I)/Au(III) catalytic cycle involving a sequence of C–X oxidative addition, C(sp²)–H auration, and reductive elimination, by employing a P,N-ligand (Me-Dalpos) on gold.¹⁷

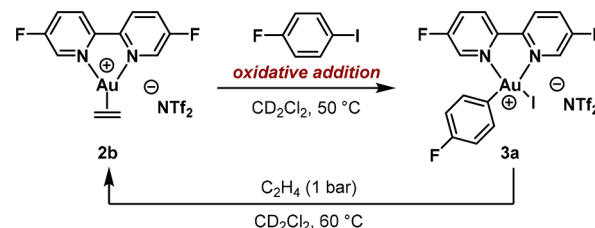
RESULTS AND DISCUSSION

At the outset of our studies, we targeted higher (>2) coordinate Au(I) complexes that might exhibit significant back-donation. Of particular interest was the chemistry of cationic [bipyAu(alkene)]⁺ complexes bearing a variety of substituted 2,2'-bipyridyl frameworks. Previous routes to such complexes are prolonged and inefficient,¹⁸ and so we sought a more effective entry, such that our investigations into downstream reactivity might be facilitated. Ultimately, we found that the target complexes can be accessed readily by addition of bipy or its derivatives to homoleptic Au(I)-alkene complexes prepared *in situ*. The gold alkene complex [Au(C₂H₄)₃][NTf₂] (**1**) was prepared in a manner analogous to that reported for [Au(C₂H₄)₃][SbF₆] (Scheme 2).¹⁹ Complex **1** is extremely

Scheme 2. Synthesis of [(κ²-5,5'-Difluoro-2,2'-bipyridine)Au(η²-C₂H₄)]⁺[NTf₂][−], **2b**

fragile, but reacts rapidly with bipy to yield [bipyAu(C₂H₄)]⁺[NTf₂][−] (**2a**). This process occurs with similar efficacy for a variety of substituted bipyridines; in particular, exposure of **1** to 5,5'-difluoro-2,2'-bipyridine (F₂-bipy) generated [(F₂-bipy)Au(C₂H₄)]⁺[NTf₂][−] (**2b**), in which the fluorine substituents provide a convenient ¹⁹F NMR spectroscopic handle for further studies. The molecular structure of **2b** was determined by single-crystal X-ray diffraction (scXRD), which revealed a distorted trigonal planar gold center with the F₂-bipy ligand adopting the symmetric κ²-mode. Most importantly, the Au–C distances are contracted and the alkene C=C bond is elongated significantly in comparison to two-coordinate [LAu(η²-alkene)]⁺ cations (L = PR₃, NHC) (see the SI).²⁰ These observations are consistent with enhanced π-back-donation enforced by the F₂-bipy ligand system. Significantly, whereas **1** is exceptionally fragile, complexes **2** show impressive stability, being handled readily in air and tolerating nonanhydrous solvents in subsequent reactions.

With ample quantities of **2b** in hand, investigations into its behavior toward aryl-halide oxidative addition were undertaken. When **2b** was exposed to 4-fluoriodobenzene (2 equiv) at 50 °C in CD₂Cl₂, the solution changed rapidly from colorless to pale yellow color (Scheme 3). Moreover, the ¹⁹F NMR

Scheme 3. Reaction of **2b** with 4-Fluoriodobenzene to Give [(F₂-bipy)Au(4-F-C₆H₄)I]⁺[NTf₂][−], **3a**

spectrum showed three new multiplets in a 1:1:1 ratio, consistent with oxidative addition to give [(F₂-bipy)Au(4-F-C₆H₄)I]⁺[NTf₂][−] (**3a**). Further confirmation was obtained by analysis of the reaction mixture using high-resolution electrospray ionization mass spectrometry (ESI-HRMS). An ion was observed with *m/z* 610.9482, which is in agreement with the calculated *m/z* for the [(κ²-F₂-bipy)Au(4-F-C₆H₄)I]⁺ ([**3a** – NTf₂]⁺) cation (610.9501). Subsequently, the molecular structure of **3a** was confirmed unequivocally by scXRD, with the Au(III) center adopting a slightly distorted square planar geometry, as expected for a d⁸ metal (Figure 1). Given subsequent observations (*vide infra*), it is important to note that the C–I bond has clearly been broken in a formal oxidative addition reaction.

The promise of our initial observation of oxidative addition to afford **3a** was tempered by the fact that the conversion was only around 10%. By increasing the aryl iodide loading from 2 to 20 equiv an increased conversion of 35% was observed after

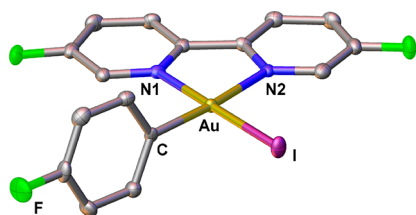


Figure 1. Molecular structure of the cation of **3a**. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms and the NTf₂ anion have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Au–C 2.011(3), Au–I 2.5357(3), Au–N1 2.080(3), Au–N2 2.130(3), N1–Au1–N2 78.92(12), N(2)–Au–I 99.37(8), N(1)–Au–C 95.17(14), C–Au–I 86.54(11).

6 h at 50 °C. Raising the temperature to 80 °C increased the consumption of **2b**, but full conversion to **3a** could still not be achieved. ¹⁹F NMR spectroscopy revealed that conversion reaches a plateau at 40–60 °C, whereas higher temperatures (70 or 80 °C) lead to decomposition of **3a** (see the SI). We hypothesized that **3a** may be in equilibrium with Au(I)-ethylene complex **2b** (i.e., that oxidative addition may be reversible), and hence we devised experiments to explore this most interesting proposition. We reasoned that if oxidative addition to **2b** is reversible, then removal of free ethylene from the reaction mixture should drive the equilibrium to the right. Thus, a solution of **2b** and 4-fluoroiodobenzene (20 equiv) was heated to 50 °C in a sealed tube under a static vacuum (approximately 10^{−2} mbar). Remarkably, using this simple modification, full conversion to **3a** was observed (¹⁹F NMR) after 1 h. To confirm the reversibility of the oxidative addition process, a solution of **3a** was pressurized (1 bar) with ethylene, and this resulted in >95% conversion to **2b** after 1 h at 60 °C (Scheme 3). This latter result also provides unambiguous confirmation of the feasibility of C(sp²)–I reductive elimination from complex **3a**.²¹ That **2b** and **3a** lie in a finely balanced equilibrium contrasts sharply with both the oxidative addition behavior of Pd(0) complexes toward aryl iodides and the work of Amgoune and Bourissou (Scheme 1B).¹⁴

The apparent differences in reactivity between **2a/b** and Amgoune and Bourissou's carboranyl diphosphine system (Scheme 1B) prompted us to explore the potential energy surface for the oxidative addition step using density functional theory (Figure 2, black pathway). Starting from the ethylene complex, **2a**, initial substitution of C₂H₄ by a representative electron-deficient aryl iodide, 4-CF₃-iodobenzene, to form an η²-arene complex is moderately endothermic (ΔE = +17.6 kcal/mol).²² In comparison, Joost et al. computed a value of +3 kcal/mol for the corresponding initiation step in Scheme 1B, where anionic [NTf₂][−] is displaced by 4-fluoroiodobenzene:¹⁴ the neutral ethylene ligand present in **2a/b** clearly stabilizes the Au(I) precursor more effectively than [NTf₂][−]. From the η²-arene intermediate, the oxidative addition step is moderately exothermic (ΔE = −13.2 kcal/mol), with a barrier of only 10.1 kcal/mol for the forward reaction and 23.3 kcal/mol for the microscopic reverse (C–I reductive elimination). The combination of an endothermic ligand displacement step and a moderately exothermic oxidative addition makes the overall reaction very marginally endothermic (+4.4 kcal/mol). This observation, alongside the surmountable barrier for the reverse step, is consistent with the experimental evidence for an equilibrium. Comparing again to the computed surface for Amgoune and Bourissou's 1,2-bis(diphenylphosphino)-1,2-

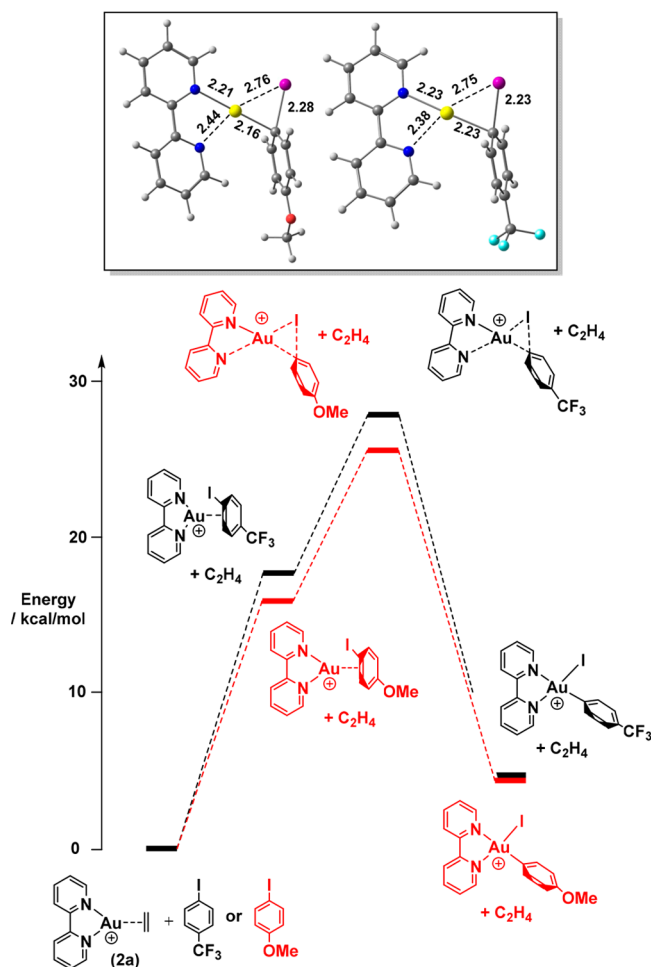
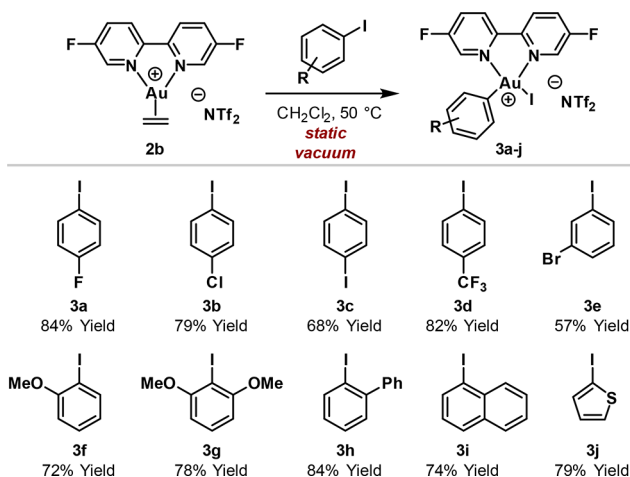


Figure 2. Computed potential energy surface for the oxidative addition reaction, starting from **2a**. Calculations were performed using the ωB97-XD functional, a def2-TZVP basis with associated 60-electron pseudopotential on Au, def2-SVP with associated 28-electron pseudopotential on I, def2-SVP on C/N, and def2-SV on H/O/F. The effects of solvent were incorporated using the SMD solvation model (CH₂Cl₂ solvent). Energies shown include zero-point corrections. The inset compares the transition structure for the reaction with 4-OMe-iodobenzene (L) and 4-CF₃-iodobenzene (R).

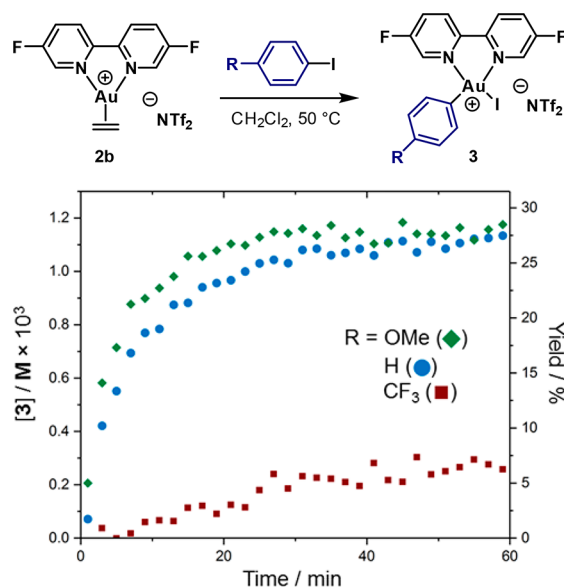
dicarboclosododecarborane-ligated system,¹⁴ the most conspicuous difference appears to be the relative stability of **2a/b** compared to LAu-NTf₂.

With conditions in hand for the efficient oxidative addition of 4-fluoroiodobenzene to **2b**, we explored the scope of the reaction with respect to the aryl iodide component (Table 1). Within 1–6 h at 50 °C, full conversion to the corresponding Au(III) complex was observed with a range of aryl iodides, as determined by ¹⁹F NMR spectroscopy. Both electron-rich (**3f/g**) and electron-poor (**3d**) aryl iodides are tolerated, as well as substrates with bulky groups adjacent to iodine (**3f/g/h**). Furthermore, heteroaromatic (**3j**) and halide-containing substrates (**3b/c/e**) are also compatible. For **3b** and **3e**, the high selectivity of **2b** toward the C–I bond is significant; no competing C–Cl/Br oxidative addition was observed. Oxidative addition products **3a–j** were isolated in good to excellent yields and were characterized by ESI-MS, ¹H NMR, and ¹³C NMR spectroscopies. The molecular structures of complexes **3b/c/f/h/j** were also confirmed by scXRD. These complexes are air stable for days at room temperature and stable for

Table 1. Scope of Aryl Iodide Oxidative Addition to **2b**^a^aIsolated yields are quoted.

months at -20 °C. So far, attempts to extend the oxidative addition behavior beyond aryl iodides have not been successful; studies on this aspect are ongoing. We have also confirmed that the oxidative addition behavior is not specific to F_2 -bipy complex **2b**. Indeed, **2a** reacts with 4-fluoriodobenzene (CH_2Cl_2 , 3 h, 50 °C), giving $[(\kappa^2\text{-}2,2'\text{-bipy})\text{Au}(\text{4-F-C}_6\text{H}_4\text{I})\text{NTf}_2]$ (**3k**) in 72% isolated yield; the structure of **3k** was confirmed by sXRD (see the SI). Accordingly, oxidative addition to Au(I) can be realized using cheap (approximately \$2/g) and readily available bipy.

Analysis of the relative reaction rates of oxidative addition to **2b** showed that electron-rich aryl iodides react significantly faster than electron-poor systems (initial rate order for 4-R- $\text{C}_6\text{H}_4\text{I}$: R = OMe > H > CF_3 ; Scheme 4). This order of reactivity is in agreement with the trend reported by Amgoune, Bourissou, et al. for the process outlined in Scheme 1B¹⁴ and

Scheme 4. Reaction Profiles for Oxidative Addition of 4-Substituted Aryl Iodides to **2b**^{a,b}

^aReaction progress monitored by ^{19}F NMR spectroscopy. ^bReaction conditions: 2.87 μmol of **2b**, 28.7 μmol of aryl iodide, 0.0041 M with respect to **2b** in CH_2Cl_2 under N_2 .

contrasts to the reactivity of $\text{Pd}(0)$ toward aryl iodides, where electron-poor substrates have been shown to react faster.²³ In Figure 2 we also show the computed potential energy surface for the reaction with 4-OMe-iodobenzene (Figure 2, red pathway) for comparison. While the energetic differences for the two aryl iodides (R = CF_3 vs OMe) are undeniably small, the trend is consistent with the measured rates, inasmuch as the barrier for the forward reaction is lower for 4-OMe-iodobenzene than for 4- CF_3 -iodobenzene (+9.4 vs +12.1 kcal/mol). In the two transition structures shown in the inset at the top of Figure 2, the coordination at Au is approximately linear ($\text{C}_{\text{ipso}}\text{-Au-N} = 169^\circ$), with short bonds to the *ipso* carbon and one of the two bipy nitrogen atoms. The second Au–N bond, in contrast, is much longer (~ 2.4 Å), as is the Au–I distance (~ 2.75 Å), while the C–I bond is only marginally elongated compared to 4- CF_3 -iodobenzene (2.11 Å). These structural features are collectively characteristic of an early transition state with Au(I) character, where the dominant interaction between the arene and the $[(\text{bipy})\text{Au}]^+$ fragment involves donation of electron density from the arene via the *ipso* carbon. The electron-donating methoxy group in the 4-position enhances the negative charge at the *ipso* carbon, and the result is a slightly shorter and stronger Au–C bond in the transition structure for 4-OMe-iodobenzene (2.16 Å vs 2.23 Å in 4- CF_3 -iodobenzene).

Having established that oxidative addition is facile, we undertook investigations into subsequent cross-coupling steps. Accordingly, we exposed CH_2Cl_2 solutions of complex **3a** to a variety of 4-tolyl-bearing organometallic reagents and raised the reaction temperature until reactivity was observed (Table 2).

Table 2. Reaction of **3a** with Organometallic Nucleophiles^a

entry	[M]	T/°C	3a/%	4/%	5/%	ArI/%
1	$\text{B}(\text{OH})_2$	60	53	0	0	26
2	Bpin	50	55	0	0	39
3	SiMe_3	rt	58	0	0	30
4	$[\text{B}(\text{pin})(t\text{-Bu})]\text{Li}$	-78 to rt	0	3	36	4
5	MgBr	-78 to rt	0	24	21	0
6	Li	-78 to rt	0	0	0	35
7	$\text{Sn}(n\text{-Bu})_3$	-78 to rt	0	51	9	11
8	SnMe_3	-78 to rt	0	61	0	7
9	ZnCl	-78 to rt	0	72	5	18

^aYields were determined by ^{19}F NMR spectroscopy.

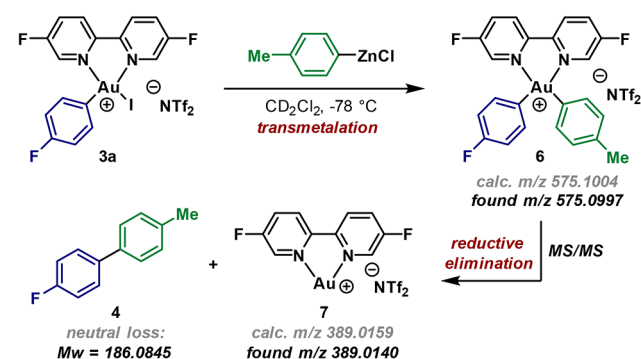
Boronic acid, boronic acid pinacol ester, and trimethylsilane-based nucleophiles showed very little reactivity (entries 1–3), and only reductive elimination to release 4-fluoriodobenzene was observed (25–40% yield). $\text{Li}[\text{4-tolylB}(\text{pin})(t\text{-Bu})]$ resulted in complete and rapid consumption of **3a**, and, promisingly, 3% of the desired cross-coupled product **4** was formed (entry 4). In this case, homocoupling predominated to generate 4,4'-difluorobiphenyl **5** in 36% yield. Nevertheless, this result suggested that other classes of organometallic reagent may favor heterocoupling to a greater extent. 4-Tolyl lithium did not give any of the desired product, but by switching to 4-

tolylMgBr we were able to form **4** in 24% yield (entries 5, 6). 4-TolylSnBu₃ and 4-tolylSnMe₃ offered further benefits, generating **4** in 51% and 61% yield, respectively (entries 7, 8); in the case of 4-tolylSnBu₃, homocoupling product **5** was also observed. Ultimately, we found that 4-tolylZnCl offered the best reactivity, providing **4** in 72% yield and with high selectivity over **5** (entry 9). This result demonstrates the feasibility of efficient fragment coupling and C–C bond formation, while also providing the first example of a Negishi cross-coupling at gold, albeit under stoichiometric conditions.

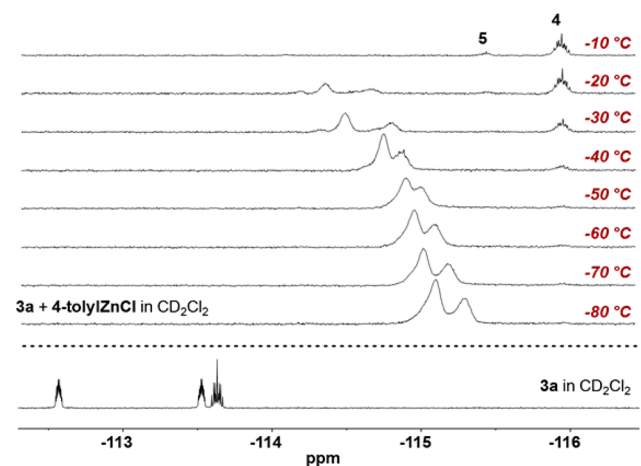
The most probable pathway for the Au-mediated Negishi coupling involves transmetalation^{16,24} of the arylzinc reagent with **3a** to give intermediate **6**, which undergoes reductive elimination to release **4** and generate complex **7** (Scheme 5A).

Scheme 5. Transmetalation and Reductive Elimination from **3a**

(A) Tandem mass spectrometry (ESI-MS/MS):



(B) Low temperature ¹⁹F NMR spectroscopy:



To gain further evidence for these steps, we monitored the reaction of **3a** with 4-tolylZnCl by variable-temperature ¹⁹F NMR spectroscopy (Scheme 5B). This showed complete consumption of **3a** at -78 °C to give an intermediate consistent with **6**. This species was stable up to approximately -40 °C, at which point it decomposed rapidly to form **4** and a small amount of **5**. Aliquots of the reaction mixture were analyzed by ESI mass spectrometry (Scheme 5A), and an ion was observed with *m/z* 575.0997, which agrees with the calculated *m/z* for the cation of **6** (575.1004). Tandem mass spectrometry showed that this ion fragments to a new ion with *m/z* 389.0140, which corresponds to the calculated *m/z* for the cation of **7** (*m/z* 389.0159). These data amount to the direct observation of reductive elimination from **6** to give **4** and **7**.²⁵

Despite observing the formation of **7**, we have so far been unable to render the overall three-step process catalytic. We speculate that the relative conditions required for the oxidative addition (greater than 50 °C) versus the transmetalation/reductive elimination steps (operating below -30 °C), combined with the fragility of **7** under the reaction conditions, mean that decomposition occurs before subsequent reoxidation.

CONCLUSION

In summary, we show that the Au(I) complex [(F₂-bipy)Au-(C₂H₄)] [NTf₂] undergoes sequential aryl-iodide oxidative addition, aryl-zinc transmetalation, and C–C reductive elimination to provide the first example of a Au-mediated Negishi cross-coupling. Accordingly, elementary steps that are typical of Pd-catalyzed biaryl formations have now been demonstrated from a simple monometallic Au center in the absence of directing groups. The chemistry is switched on by the simple bipyridyl ligand framework, which enhances back-donation from Au to facilitate the key Ar–I oxidative addition step. The studies described here underpin our ongoing efforts to devise oxidant-free Au-catalyzed biaryl formations using readily available aryl halides as the electrophilic partner.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b01411.

Experimental details and characterization data (PDF)

Crystallographic data (CIF)

(CIF)

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Notes

The authors declare no competing financial interest.

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